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Original article

Self-assembly of supra-amphiphile of azobenzene-galactopyranoside based on dynamic covalent bond and its dual responses

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ABSTRACT

In this paper, dynamic covalent bond has been employed to construct supra-amphiphile of carbohydrate for the first time. In neutral environment, the molecule was fabricated by reacting a hydrophobic building block bearing benzoic aldehyde with a hydrophilic building block bearing hydrazine to form a sugar-containing supra-amphiphile based on acylhydrazone bond. The obtained azobenzene-galactopyranoside (Azo-Gal) supra-amphiphile self-assembled to fibrillar structure in water, which showed dual responses to UV light and pH.

1. Introduction

Supra-amphiphiles [1] refer to amphiphiles that are constructed by dynamic covalent bonds [2,3] or non-covalent interactions such as hydrogen bonding, π–π interaction, host–guest interaction and charge transfer interaction [4–6]. Generally, the hydrophilic part and the hydrophobic part can be easily linked together *via* these dynamic connections, which avoids tedious syntheses. Moreover, the supra-amphiphiles are easier to be manipulated compared with amphiphiles fabricated by covalent bonds due to the dynamic nature of the linkage. They undergo self-assembly and disassembly processes in a controllable way with stimuli-responsive properties [7,8].

Carbohydrates play an important role in a variety of biological processes, such as cell adhesion, proliferation, differentiation, recognition, inflammation and the immune response [9]. They are able to form hydrogen bonds, which makes them become important building blocks in supramolecular chemistry [10]. However, few works have been done to incorporate carbohydrates into supra-amphiphiles [11]. Zhang and co-workers constructed the first example of sugar-containing supra-amphiphile, *i.e.* supramolecular glycolipid based on host-enhanced charge transfer interaction [12]. However, as far as we know, supra-amphiphile of carbohydrate has not been achieved on the basis of dynamic covalent bond.

Herein, for the first time, construction of azobenzene-galactopyranoside (Azo-Gal) supra-amphiphile based on acylhydrazone dynamic covalent bond formed by the aldehyde of the azobenzene-containing hydrophobic domain (Azo-CHO) and the hydrazine of the sugar moiety (Gal-N_2H_4) was reported (Fig. 1). Acylhydrazone bond is stable in neutral or alkaline environment, but it can be hydrolyzed under acidic condition. Besides, azobenzene is utilized as a model hydrophobic moiety since it is a wildly used building block for self-assembly and forms reversible complex with α-CD. The Azo-Gal supra-amphiphile self-assembles into fiber in μm scale, which is featured by light and pH responsiveness.

2. Experimental

2.1. Materials and experiments

Ethyl 3-hydroxypropanoate was purchased from Maya Chemical and used as received. D-Galactose was purchased from Bangcheng Chemical and used as received. Trichloroacetonitrile, dichloromethane (DCM) and *N*,*N*-dimethylformamide (DMF) were distilled before use. Unless specially mentioned, all other chemicals were purchased from J&K Chemical and used as received. The reactions were monitored and the Rf values were determined using analytical thin-layer chromatography (TLC). The TLC plates were visualized by immersion into 5% sulfuric acid solution in ethanol followed by heating using hot air heater.

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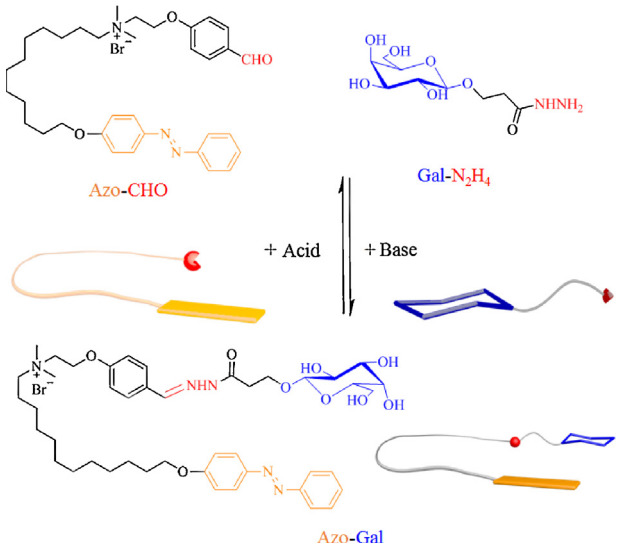

Fig. 1. An **Azo-Gal** supra-amphiphile based on a dynamic covalent bond.

Column chromatography was carried out on silica gel (200–300 mesh).

^{1}H NMR and ^{13}C NMR spectra were recorded on an AVANCE III HD 400 MHz spectrometer. The matrix-assisted laser desorption ionization time-of-flight mass spectrometry (Maldi-TOF MS) measurement was performed using a Perspective Biosystem Voyager DE-STR MALDI-TOF MS (Applied Biosystems, Framingham, MA). Transmission electron microscopy (TEM) images were taken on Tecnai G2 operating at 200 kV. Atomic force microscope (AFM) was carried out on a Bruker Multimode VIII SPM equipped with a J scanner. Dynamic light scattering studies (DLS) were conducted using Zetasizer Nano-ZS from Malvern Instruments. UV–vis spectroscopy was recorded in a conventional quartz cell (light path 10 mm) on a Perkin–Elmer Lambda 35 spectrophotometer.

2.2. Synthesis

The synthesis details of **A1**–**A3** and **G1**–**G3** are shown in Supporting information.

Synthesis of Azo-CHO: **A2** (130 mg, 0.67 mmol), **A3** (461 mg, 1 mmol) were added to acetonitrile and the mixture was refluxed overnight. After cooling down to room temperature, the solvent was evaporated under vacuum and the crude product was purified by column chromatography using EtOH/DCM (1:20) as eluent to yield 300 mg (70%) of Azo-CHO as yellow powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H), 8.03–7.79 (m, 6H), 7.57–7.36 (m, 3H), 7.03 (dd, 4H, J = 25.8, 8.8 Hz), 4.65 (s, 2H), 4.35 (s, 2H), 4.04 (t, 2H, J = 6.5 Hz), 3.75–3.55 (m, 6H), 1.94–1.77 (m, 4H), 1.56–1.21 (m, 17H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 190.62, 161.70, 152.74, 146.81, 132.16, 130.32, 129.03, 124.73, 122.51, 114.93, 114.71, 114.13, 68.34, 62.71, 62.56, 52.12, 43.95, 29.48, 29.45, 29.42, 29.38, 29.31, 29.22, 29.16, 26.29, 25.98, 22.96. Maldi-TOF MS: calcd. for $C_{35}H_{48}N_3O_3^+$ 558.37, found 558.37.

Synthesis of **G4**: A mixture of **G3** (1 g, 2 mmol), ethyl 3-hydroxypropanoate (0.186 g, 1.6 mmol) in dry DCM (15 mL) was stirred at −35 °C for 30 min under Ar atmosphere. Trimethylsilyl trifluoromethanesulfonate (TMSOTf, 140 μL, 0.77 mmol) was added dropwise to the mixture while stirring. Then the mixture was stirred at −35 °C until the complete disappearance of the starting material **G3** (using the TLC to monitor the reaction process). Then the reaction was quenched by adding triethylamine. After the reaction mixture was recovered to the ambient temperature, it was concentrated under vacuum. The product was purified by column chromatography using EtOAc/petroleum ether (1:2) as eluent to yield 0.3 g (42.5%) of **G4** as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.39 (dd, 1H, J = 3.4, 1.1 Hz), 5.18 (dd, 1H, J = 10.5, 7.9 Hz), 5.01 (dd, 1H, J = 10.5, 3.4 Hz), 4.52 (d, 1H, J = 8.0 Hz), 4.19–4.10 (m, 5H), 3.96–3.81 (m, 2H), 2.65–2.56 (m, 2H), 2.15 (s, 3H), 2.05 (d, 6H, J = 0.8 Hz), 1.98 (s, 3H), 1.27 (t, 3H, J = 7.1 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.02, 170.39, 170.25, 170.15, 169.46, 101.53, 70.85, 70.65, 68.64, 67.00, 65.54, 61.24, 60.58, 34.83, 20.71, 20.66, 20.58, 14.17.

Synthesis of Gal-N_2H_4: A mixture of **G4** (0.7 g, 1.56 mmol), 85% hydrazine hydrate (0.59 g, 15.7 mmol) in ethanol was stirred at ambient temperature for 1 d until the complete disappearance of the raw material of **G4** and appearance of the product (using the TLC to monitor the reaction process). The mixture was concentrated under vacuum and was purified by column chromatography using water/acetonitrile (1:2) as eluent to yield 0.2 g (48.8%) of Gal-N_2H_4 as white solid. ^{1}H NMR (400 MHz, D_2O): δ 4.26 (d, 1H, J = 7.9 Hz), 4.01 (dt, 1H, J = 10.8, 6.0 Hz), 3.85–3.77 (m, 2H), 3.64 (qd, 2H, J = 11.7, 6.1 Hz), 3.54 (ddd, 2H, J = 13.4, 8.9, 3.8 Hz), 3.37 (dd, 1H, J = 9.9, 7.9 Hz), 2.42 (t, 2H, J = 6.0 Hz). ^{13}C NMR (101 MHz, D_2O): δ 172.78, 102.83, 75.10, 72.64, 70.60, 68.57, 65.80, 60.95, 34.36. Maldi-TOF MS: calcd. for $C_9H_{18}N_2O_7$ 266.11, found 266.29 (289.29-Na^+23).

2.3. Preparation of Azo-Gal supra-amphiphile

Mixing Azo-CHO and Gal-N_2H_4 together in the molar ratio of 1:1 in DMSO for 3 days until the complete formation of Azo-Gal and then stored as original solution. Ultrasound or heating accelerates the formation speed.

2.4. Self-assembly of Azo-Gal supra-amphiphile

Deionized water (8 mL) was added into the DMSO solution of Azo-Gal (1 mL, 1 mg/mL) dropwise by using a syringe pump at the rate of 20 mm/h under vigorous stirring. Then the solution was dialyzed (MWCO 1000) against deionized water to remove the extra DMSO. Concentration of the solution was fixed at 0.1 mg/mL by adding extra deionized water.

3. Results and discussion

3.1. Preparation of the Azo-Gal supra-amphiphile

First, the two new precursors of Azo-Gal, Azo-CHO and Gal-N_2H_4 were synthesized separately. As shown in Scheme 1, Azo-CHO was prepared *via* four steps. First, 4-hydroxybenzaldehyde reacted with 1,2-dibromoethane in the presence of K_2CO_3 affording compound **A1**. Then **A1** was treated with dimethylamine hydrochloride in the presence of K_2CO_3 to afford compound **A2**. Meanwhile, compound **A3** was synthesied by reacting 4-phenylazophenol with 1,12-dibromododecane in the presence of K_2CO_3. In the end, through the reaction between **A2** and **A3**, the final product Azo-CHO was formed. On the other hand, Gal-N_2H_4 was synthesized *via* five steps following the classical glycosylation strategy. First all of the hydroxy groups of galactose were protected by acetyl groups. After selectively deprotecting the acetyl group on the anomeric carbon followed by reacting with trichloroacetonitrile, galactosyl trichloroacetimidate was synthesized. Compound **G4** was prepared *via* glycosylation of ethyl 3-hydroxypropanoate with the galactosyl trichloroacetimidate and was transformed to the final product of Gal-N_2H_4 with hydrazine hydrate in ethanol.

After mixing the synthesized Azo-CHO and Gal-N_2H_4 in DMSO, the dynamic covalent bond formed, which was confirmed by ^{1}H NMR. The spectrum of the mixture of Azo-CHO and Gal-N_2H_4 in